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The effect of country of origin on the properties of dicalcium phosphate dihydrate powder

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Summary

Five brands of dicalcium phosphate dihydrate powder manufactured in Germany, Japan, Spain, U.K. and U.S.A. have been characterized by X-ray diffraction, IR, DSC and TGA. Results on dehydration behaviour showed the Japanese material to be significantly more stable than the other four materials. SEM and laser scattering results showed these other four materials to be very similar, and to differ from the Japanese material, as regards micromeritic characteristics. Differences in specific surface values, as measured by adsorption of nitrogen, are related to particle size and intraparticle porosity. The above differences give rise to differences in their compression and flow properties, which could be relevant to the use of these products as excipients for solid dosage forms.

Introduction

Dicalcium phosphate dihydrate (DCPD) is widely used as an excipient in solid dosage forms. Specifically, it is one of the commonest insoluble diluents in wet granulates for capsule and tablet manufacture because it has low hygroscopicity, increases the mechanical strength of tablets and is chemically stable. Also, modified forms are available that are suitable for direct compression formulations (Bandelin, 1989; Fischer, 1992).

DCPD is usually obtained from calcium oxide, carbonate or hydroxide by precipitation with phosphoric acid (Fischer, 1992). Certain properties of the finished product depend heavily on the characteristics of the precipitation process, temperature and precipitation rate especially (Boullé and Dupont, 1955). Such properties include crystal structure, particle size and shape, particle aggregation structure and, in particular, susceptibility to dehydration at low temperatures in the presence of water vapour (Dugleux and Sallier Dupin, 1967a,b; Carstensen, 1988). The latter

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property is clearly relevant to the choice of conditions for the storage and processing of DCPD, and is known to be the chief cause of changes on storage in the physical properties and release characteristics of tablets formulated with DCPD (Patel et al., 1988; Shiromani and Bavitz, 1988; Udela and Aly, 1988).

There are currently numerous commercial sources of DCPD. In view of the above-mentioned dependence of its properties on the details of the manufacturing process, we have compared the characteristics of DCPD powders produced by five different companies in five different countries so as to establish the extent of intermanufacturer variability and estimate the repercussions for its use as a diluent in solid dosage forms.

Materials and Methods

Materials

The five DCPDs studied were samples from Merck (Germany), Kyowa (Japan), Probus (Spain), Calipharm (U.K.) and Monsanto (U.S.A.).

Powder X-ray diffraction

Measurements were carried out at room temperature on a Siemens D5000 X-ray diffractometer using monochromatic CuKα radiation and scanning from 3 to 73° 2θ at a rate of 0.25° 2θ/min. Samples were prepared by pressing into a sample holder and smoothing with a glass slide.

Infrared spectroscopy

Infrared spectra in the 200–4000 cm^{-1} region were recorded on a Mattson Cignus 100 spectrophotometer using KBr pellets.

Thermogravimetric analysis

The temperature dependence of the weight of DCPD samples was determined on a Mettler TG 50 thermobalance linked to a TC 10a processor (Mettler Instruments, Griefensee, Switzerland). Powder samples weighing 40–60 mg were heated from 50 to 250°C at a rate of 10°C/min. The results were used to calculate the activation energy of each dehydration stage from the Arrhenius equation (Dugleux et al., 1965).

Differential scanning calorimetry

DSC thermograms of 0.5–3.0 mg DCPD samples were recorded at a heating rate of 10°C/min in a Mettler DSC 30 linked to a TC 10a processor, either in an open aluminium pan under a 100 ml/min current of nitrogen or in a hermetically sealed pan. The enthalpy of each dehydration stage was determined by integration of the thermogram peaks.

Immersion calorimetry

Immersion calorimetry measurements were performed in duplicate in a Tronac Model 458 Solution Calorimeter as described by Parker and Rowe (1991).

Scanning electron microscopy

Samples were mounted on double-sided tape on aluminium stubs, coated with gold under vacuum and examined under an ISI 60 scanning electron microscope.

Particle size analysis

Particle size distributions were determined in triplicate using a Coulter LS 100 Laser Scattering Particle Size Analyser. The results are expressed in terms of mean surface diameter (d_s).

Nitrogen adsorption

Samples degassed by heating in vacuo for 24 h at 60°C and a pressure of 10^{-3} mmHg were exposed to nitrogen at 77 K and relative pressures of 0.01–0.98 in a Micromeritics ASAP 2000 apparatus. Specific surface areas S_w were calculated from the formula:

$$S_w\ (m^2\ g^{-1}) = 4.37 V_m\ (cm^3\ g^{-1})$$

where V_m is the volume of nitrogen necessary to form a monolayer, which can be calculated from the BET equation (Stanley-Wood et al., 1990). Pore size distributions were calculated from the nitrogen adsorption isotherms by the BJH method (Stanley-Wood, 1983).

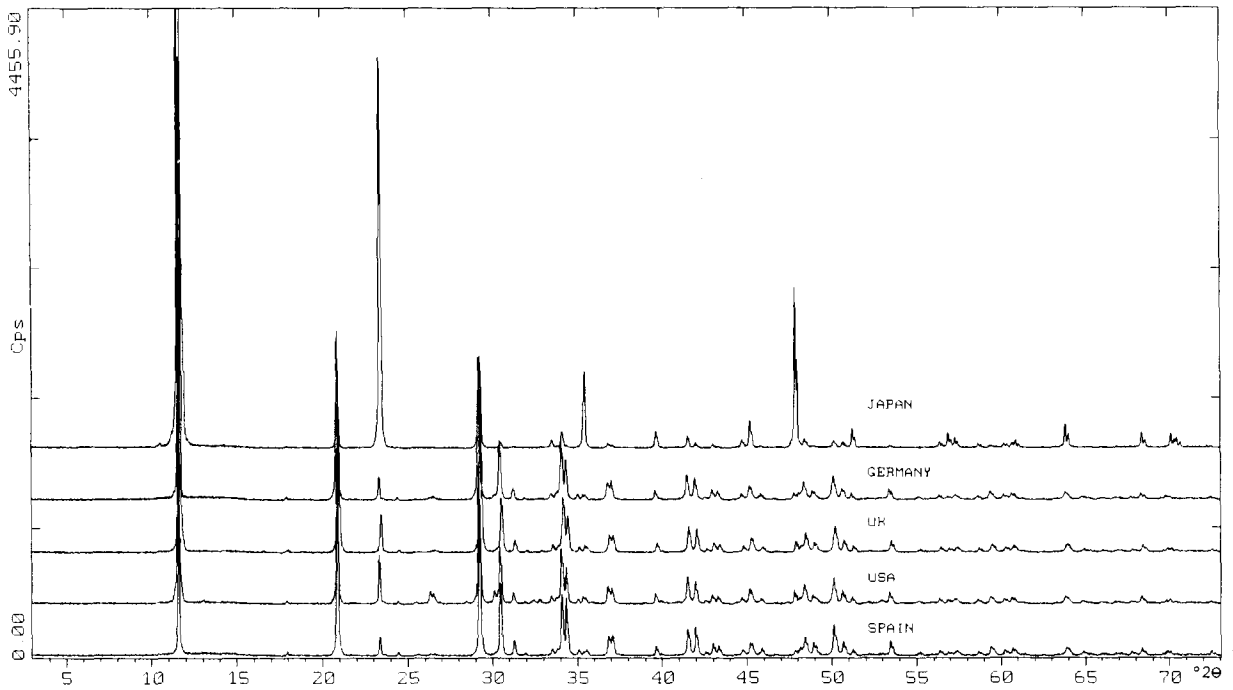


Fig. 1. X-ray diffraction scans of the DCPDs studied.

True density

True particle densities were determined in triplicate using a Quantacrome Model PY2 helium pycnometer.

Bulk density

Tapped bulk density was measured in a Hosokawa powder tester under tapping at 50 taps/min for up to 20 min. The results were used

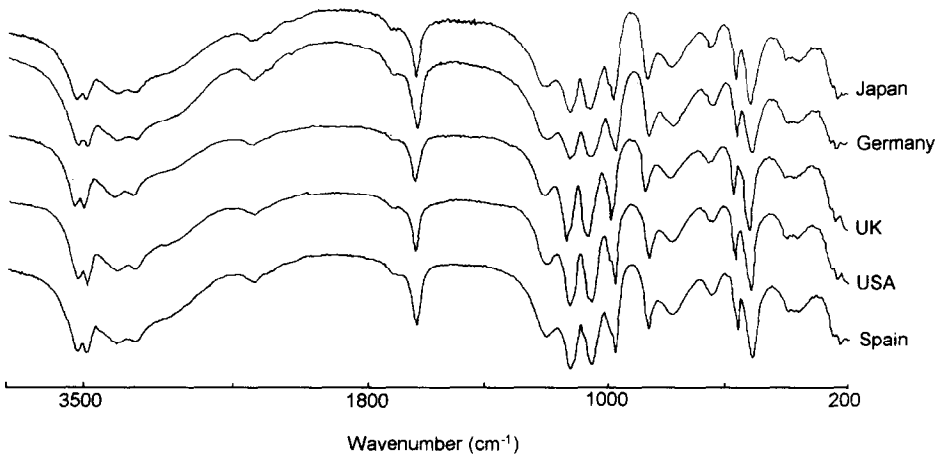


Fig. 2. IR spectra of the DCPDs studied.

to calculate compressibility and flowability index (Thomson, 1984).

Compression properties

Samples were compressed in a Korsch EKO excentric press equipped with Kistler 9031A piezoelectric pressure transducers and interfaced to a Hewlett-Packard 85 computer via an HP-IB data monitoring system (Martínez-Pacheco et al., 1985). The die wall and punch faces were lubricated with a 5% w/w suspension of magnesium stearate in acetone. Mean yield pressures under load were determined using Heckel plots of the data for compression force-displacement cycles (Humbert-Droz et al., 1982).

Results and Discussion

The X-ray diffraction spectrum of the Japanese DCPD (Fig. 1) coincides almost exactly with the available data for the natural mineral brushite, JCPDS pattern 11-293 (JCPDS, 1989), the minor differences being attributable to a preferred orientation effect. The spectra of the other DCPDs studied (Fig. 1) coincide with the data for synthetic brushite, JCPDS pattern 9–77 (JCPDS, 1989). This suggests the existence of significant structural differences between the Japanese material and the others.

The IR spectra (Fig. 2) show that all the DCPDs contained both strongly bound lattice water (appearing as bands at 663, 3488 and 3522 cm^{-1}) and weakly bound water appearing as bands at 3158 and 3268 cm^{-1} (Lecomte et al., 1955; Fraissard et al., 1965). Loss of lattice water has been reported by Dugleux and Sallier Dupin (1967a,b) to occur as follows:

$$4CaHPO_4 \cdot 2H_2O + H_2O \rightarrow Ca(H_2PO_4)_2 + Ca_3(PO_4)_2 + 9H_2O$$

$$Ca(H_2PO_4)_2 \rightarrow CaHPO_4 + H_3PO_4$$

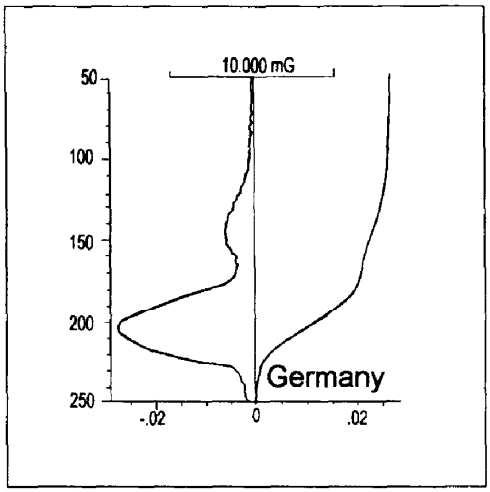
$$H_3PO_4 + CaHPO_4 \cdot 2H_2O \rightarrow Ca(H_2PO_4)_2 + 2H_2O$$

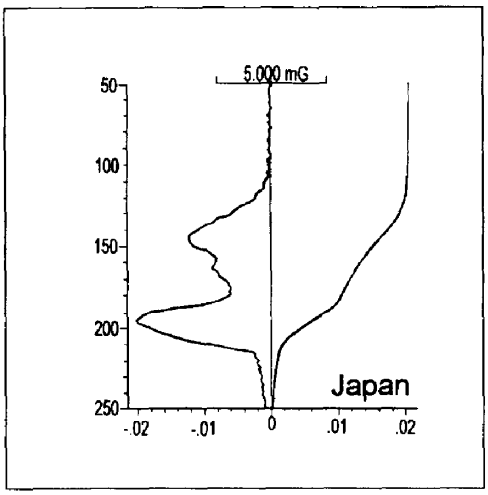
The dehydration of DCPDs, which is relevant to its pharmaceutical use, thus depends heavily on ambient humidity. It has also been reported to depend on the manufacturing process (Carstensen, 1988). In this study, thermogravimetric analysis (TGA) showed that the Japanese material, owing to its smaller adsorbed water content, lost significantly less weight below 100°C than the other materials (Table 1). In all samples, dehydration occurred in two stages (Fig. 3) (Boullé and Jolibois, 1948), but the relative contributions of each were different for the Japanese material compared to the others, possibly due to differences in structure and manufacturing procedure (Boullé and Dupont, 1955). Note that the Japanese material had the greatest total water content while the U.S.A. material failed to reach the stoicheiometric level. The observed activation energies (Table 1) show that, for both dehydra-

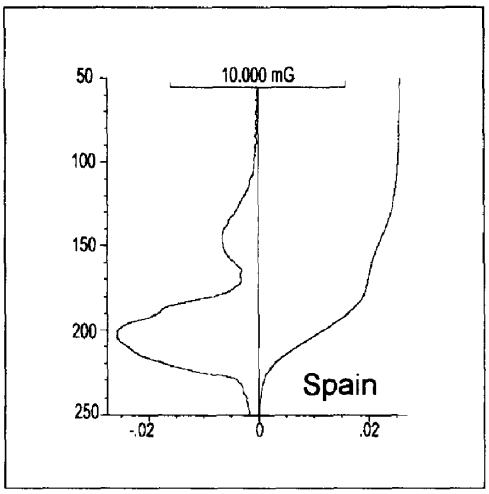
TABLE 1

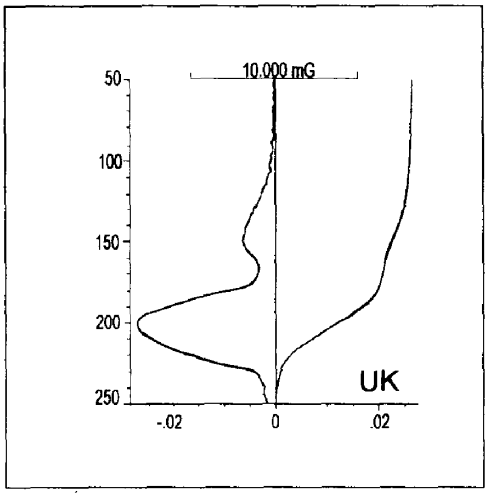
DCPD characteristics obtained from TGA and DSC curves

Source	TGA						DSC		
	Weight loss (% w/w)				Activation energy ($J\ mol^{-1}$)		Enthalpy, open pan ($J\ g^{-1}$)		Enthalpy, sealed pan ($J\ g^{-1}$)
	100°C	1st step	2nd step	Total	1st step	2nd step	1st step	2nd step	1 step
Germany	0.57	3.86	17.11	20.97	73.67	133.50	52.85	438.57	480.83
Japan	0.20	9.79	11.75	21.54	144.74	248.25	179.50	337.70	502.25
Spain	0.43	4.20	17.27	21.47	87.40	114.71	74.74	449.44	498.55
U.K.	0.45	3.82	17.38	21.20	72.52	143.93	57.61	454.00	463.57
U.S.A.	0.56	3.71	15.86	19.57	59.58	129.81	63.13	412.15	424.90









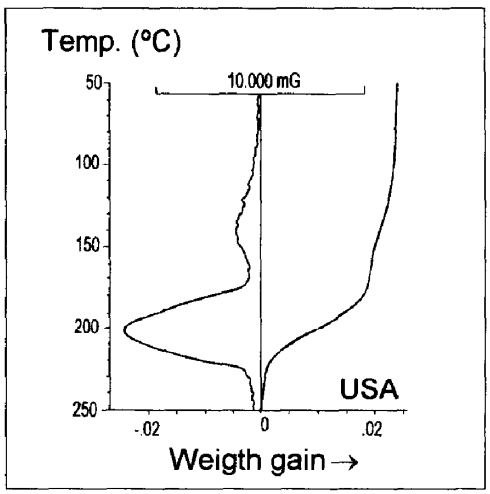


Fig. 3. TGA curves of the DCPDs studied.

tion steps, the Japanese material was the most stable.

Differential scanning calorimetry (DSC) was performed both with samples in sealed pans and with samples in an open pan under nitrogen so as to evaluate the influence of humidity and hence the involvement of autocatalysis phenomena (Dugleux and Sallier Dupin, 1965, 1967a,b). The open-pan DSC thermograms (Fig. 4) confirm the occurrence of two dehydration stages (at approx. 135–140 and 200°C), and that the first stage contributes more to the overall dehydration process in the Japanese material than in the others; the corresponding energy consumption data are related with the activation energies calculated from the TGA results (Table 1). The closed-pan thermograms, on the other hand, show a single peak (Rabatin et al., 1960; Dugleux and Sallier Dupin,

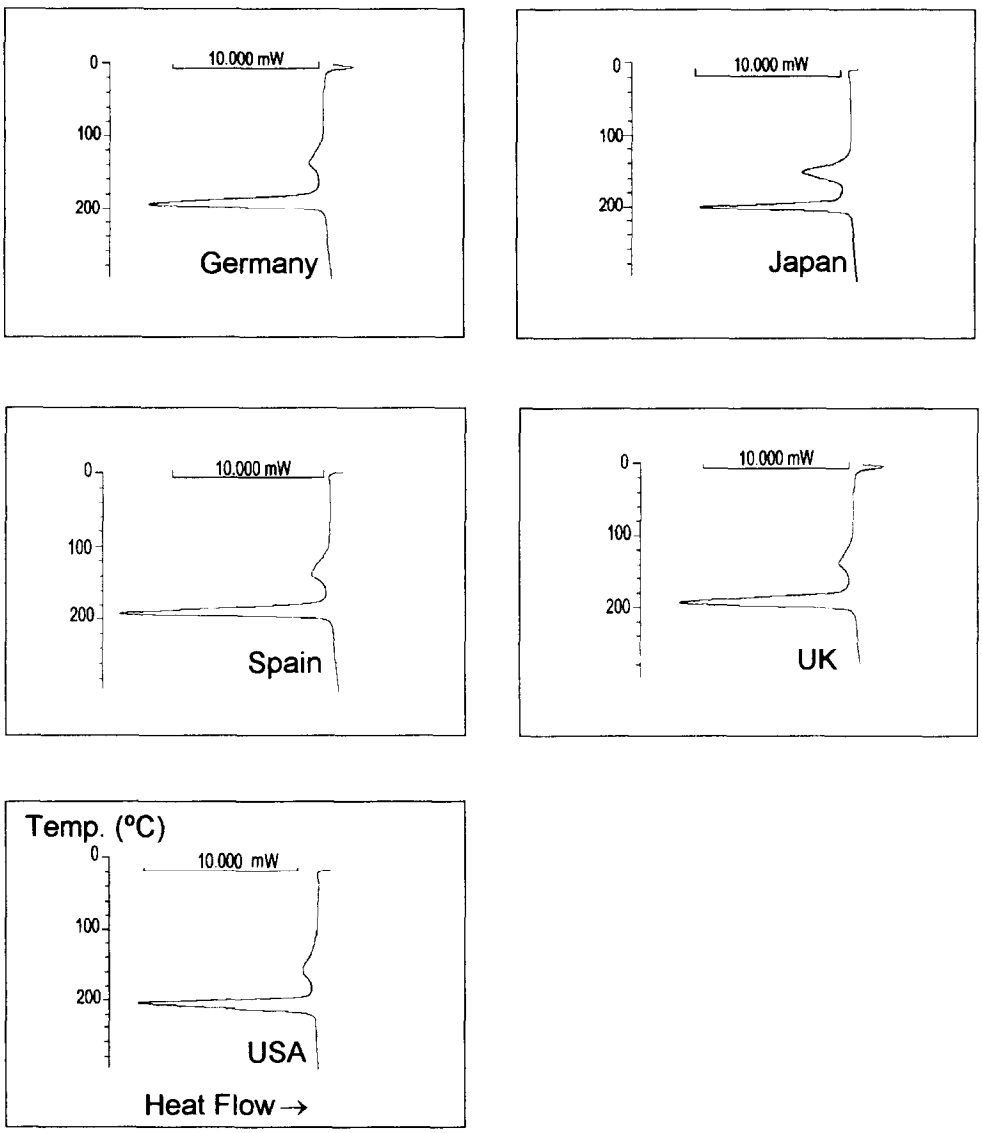


Fig. 4. DSC thermograms of DCPD samples in open pans under nitrogen.

1965) located at the same temperatures as the first of the open-pan peaks and integrating to approximately the sum of the two open-pan peaks (Table 1). These results confirm the above-mentioned influence of environmental humidity on the dehydration of DCPD.

DCPD-water interaction at the DCPD surface was investigated by immersion calorimetry. The

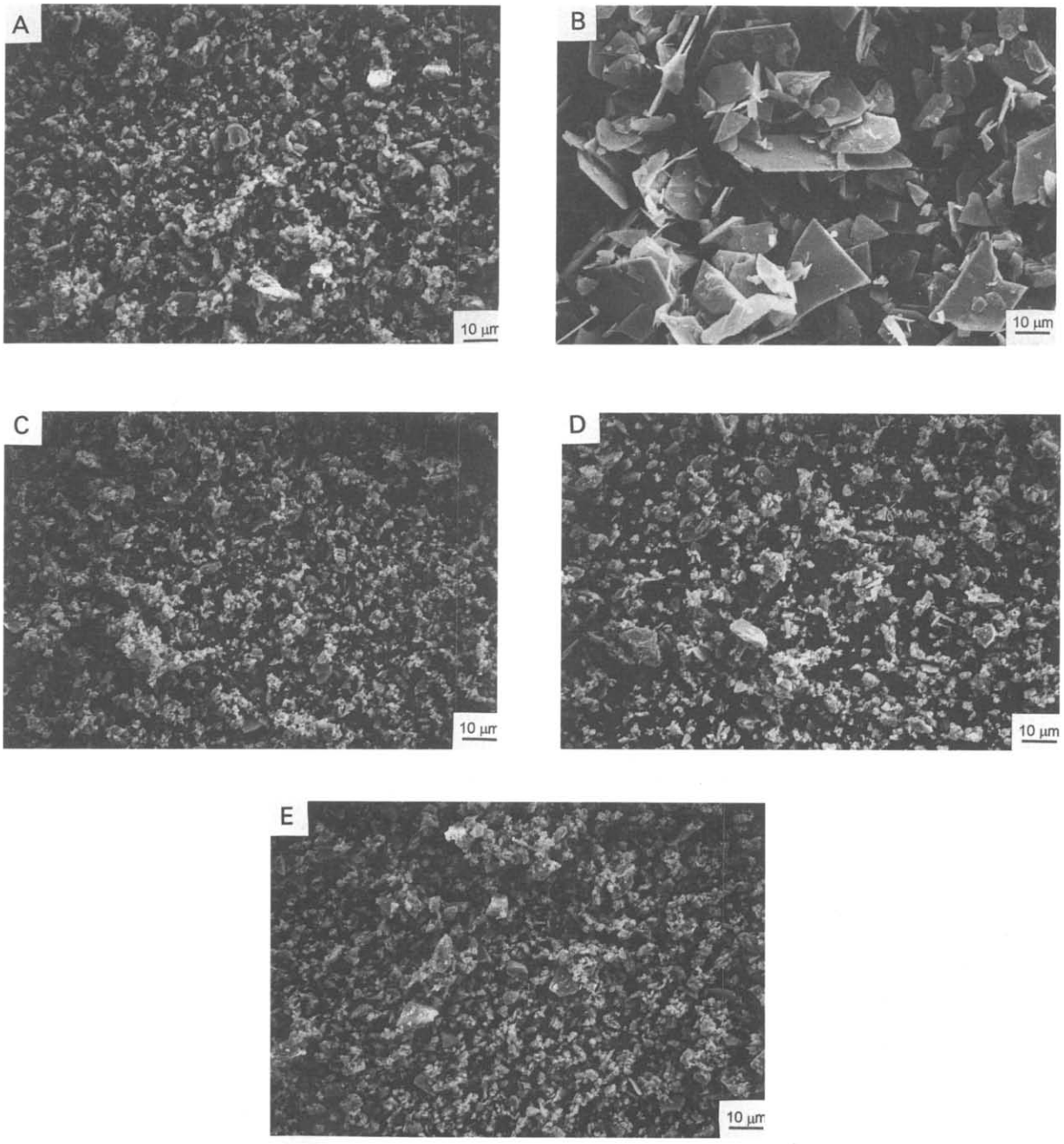


Fig. 5. Electron micrographs of samples of the DCPDs studied: (A) Germany; (B) Japan; (C) Spain; (D) U.K.; (E) U.S.A..

TABLE 2

Mean enthalpies of immersion per unit mass and per unit surface area of DCPDs studied (standard deviations in parentheses)

Source	Enthalpy of immersion	
	$-J\ g^{-1}$	$-J\ m^{-2}$
Germany	0.59 (0.05)	0.25 (0.02)
Japan	0.31 (0.05)	0.32 (0.02)
Spain	0.66 (0.16)	0.32 (0.03)
U.K.	0.53 (0.13)	0.28 (0.07)
U.S.A.	0.47 (0.04)	0.24 (0.07)

TABLE 3

Mean particle sizes and specific surface areas of the DCPDs studied (standard deviations in parentheses)

Source	Particle size (μm)	Surface area ($m^2\ g^{-1}$)
Germany	4.82 (0.08)	2.38 (0.02)
Japan	32.93 (0.12)	0.98 (0.08)
Spain	4.21 (0.24)	1.76 (0.04)
U.K.	5.09 (0.11)	1.89 (0.07)
U.S.A.	4.28 (0.01)	1.98 (0.05)

specific enthalpies of immersion determined were all very small, as expected for this material (Zografi, 1988), and their mutual differences can be attributed to differences in specific surface area, since the enthalpies per unit area were all very similar (Table 2). The five materials are therefore equivalent as regards surface energy.

SEM showed that the Japanese DCPD consisted of relatively large individual particles, whereas the other four consisted of aggregates of smaller particles (Fig. 5). The difference in particle size was confirmed by laser scattering particle size analysis (Table 3). In keeping with these findings, the specific surface area of the Japanese material, as determined from nitrogen adsorption measurements, was smaller than those of the other materials (Fig. 6 and Table 3). The fact that the latter differ mutually much more widely than do the particle sizes of these four materials (in particular, the German product has a much larger specific surface area than the others) is explained by their different intraparticular porosities (Fig. 7; note the very low porosity of the Japanese material).

TABLE 4

Mean flow and densification characteristics of the DCPDs studied (standard deviations in parentheses)

Source	Compressibility (%)	Flowability index	Mean yield pressure (MPa)
Germany	53.2	36	353.1 (4.2)
Japan	49.7	46	344.4 (14.9)
Spain	53.3	39	350.8 (8.3)
U.K.	54.8	39	348.4 (8.3)
U.S.A.	53.8	39	343.4 (21.8)

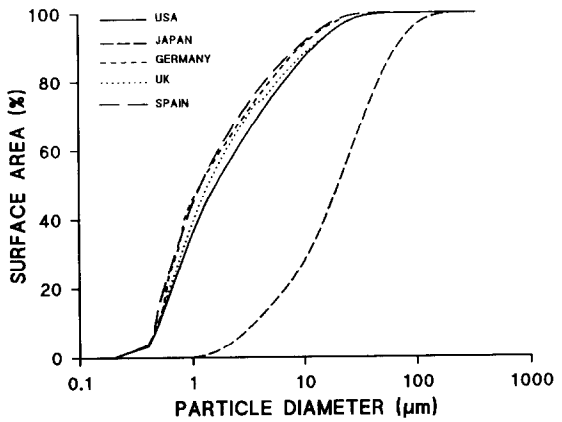


Fig. 6. Particle size distributions determined by laser light scattering.

The above granulometric characteristics of the five DCPDs studied are reflected in their compressibilities and flowability index, the Japanese

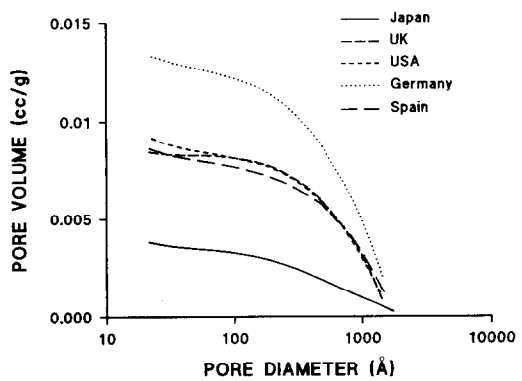


Fig. 7. Pore size distributions calculated from nitrogen adsorption isotherms by the BJH method.

material being significantly less compressible and more fluid than the others (Table 4). However, the five products did not differ significantly as regards mean yield pressure (obtained from Heckel plots), doubtless because the chief mechanism involved in their densification is in all cases particle fragmentation (Humbert-Droz et al., 1982).

Conclusions

The salient feature of the above results is that the Japanese DCPD differs markedly from the other four as regards, in particular, the binding of the associated water and the size and shape of the DCPD particles. These differences are presumably attributable to differences in manufacturing process. With regard to their relevance to the use of DCPD as an excipient in solid dosage forms, it is possible that these differences may affect not only the flow characteristics investigated in this work, but also the chemical stability of certain active principles and the physical stability of the dosage forms.

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